

REMARKS

Reconsideration of the present application is respectfully requested for the reasons that follow.

Rejections under 35 USC § 112, first paragraph

Claims 5, 22-24, 28-33 and 39-59 are pending in the application. The Examiner has rejected claims 22-24, 28-31, 43-46, 49-51 and 55-56 under 35 USC § 112, first paragraph, as failing to comply with the written description requirement. This is a new matter rejection and the Examiner has based the rejection on the last amendment to claim 22. Specifically, the Examiner argues that there is no support in the specification for the claim element “effective to produce elevated levels of CldUMP and CldU” in a tumor. The Examiner argues further that there is only support in the specification for administering 5-chloro-2'-deoxycytidine and tetrahydrouridine in amounts that sensitize a tumor to radiation. Applicant disagrees with the Examiner's assertions. The specification (see p. 13, ll. 12-13) indicates “... high doses of CldUMP formed from CldC in tumors ...”, thus providing sufficient written description support for the CldUMP element. In addition, because CldU is converted into CldUMP, it is inherent that the CldU must have been present in the tumor in elevated levels or there would not have been sufficient amounts available for thymidine kinase to convert it into CldUMP. Therefore, there is sufficient written description support for the subject claim elements, and this rejection should be withdrawn.

Rejections under 35 USC § 102(b)

The Examiner has rejected claims 22-24, 28-29, 32, 39, 42-44 and 47 under 35 USC § 102(b) as being anticipated by Greer (WO 85/01871). The Examiner argues that Greer teaches a method of sensitizing neoplastic tissue to radiation comprising the administration of 5-CldC and H₄U to a patient. The Examiner also argues that Greer further teaches that CldC should be converted preferentially at the tumor site to CldUMP in human tumors possessing high levels of deoxycytidine kinase and dCMP deaminase. Thus, the Examiner continues, Greer anticipates the element of claim 22 involving administering CldC and H₄U to a tumor which results in elevated levels of CldUMP and CldU in the tumor. Additionally, the Examiner asserts that Greer anticipates sensitizing neoplastic tissue to radiation comprising the administration of 5-CldC and H₄U without pretreatment with an inhibitor of pyrimidine biosynthesis because Greer inherently discloses that the administration of the combination of 5-CldC and H₄U sensitizes tumors.

The Examiner also argues that Greer anticipates the second element of claim 22; that is, exposing a patient to an effective level of radiation to delay the growth of said tumor. Specifically, the Examiner argues that this claim element is anticipated in Greer's teaching of administering various radiation sources to patients having tumors.

Applicant does not agree with the Examiner's characterization of the anticipation rejection based on Greer. However, to expedite the issuance of these claims, independent claims 22 and 32 have been amended to require an

additional step of treating the tissue surrounding the tumor and any post-radiation surviving tumor cells with the drug combination. There is written description support for these amendments in the specification (see p. 26, para. 4 through p. 27, para. 2). Greer does not anticipate these newly amended claims because Greer does not teach any post-radiation treatment for tissue surrounding a tumor, nor for tumor cells that survive radiation treatment. In addition, it would not be inherent that a radiation treatment protocol would be followed by an additional drug treatment protocol. Therefore, these amendments render the claims not anticipated by Greer and this rejection should be withdrawn.

Rejections under 35 USC § 103(a)

The Examiner has rejected claims 30-31 and 40-41 under 35 USC § 103(a) as being obvious over Greer (WO 85/01871) in view of Shepherd (Cancer, 1992). Shepherd is directed to the treatment of patients with primary hepatocellular carcinoma with yttrium-90 microspheres. The Examiner argues that Shepherd teaches the use of yttrium-90 needles as a radiation source, which is not taught by Greer, thus rendering these claims obvious.

The Examiner has rejected claims 33, 45-46, 48, 50-51, 53-56 and 58-59 under 35 USC § 103(a) as being obvious over Greer (WO 85/01871). The Examiner argues that Greer does not explicitly teach the treatment of specific tumors as recited in the instant claims, nor does Greer teach that the treatment of the tumors results in gene silencing. However, the Examiner argues, that one of

skill in the art would be able to apply the teachings of Greer to the treatment of various tumors, thus rendering these claims obvious.

The Examiner has rejected claims 49, 52 and 57 under 35 USC § 103(a) as being obvious over Greer (WO 85/01871) in view of Nagatake (Cancer Research, 1996). Nagatake is directed to study results determining that aberrant hypermethylation occurs at the bcl-2 locus in non-small cell lung cancers. The Examiner argues that Nagatake teaches that the treatment of a tumor is associated with hypermethylation, which is not taught by Greer, thus rendering these claims obvious.

Independent claims 22 and 32 have been amended as discussed above. Neither the Shepherd reference nor the Nagatake reference discloses the step of additional drug treatment following radiation treatment and thus they cannot render the subject claims obvious over Greer. In addition, it would not be obvious to one of skill in the art to treat post-radiation surviving tumor cells with a drug combination that is known in the art as only a radiation-sensitizer.

Furthermore, Applicant would like to point out that tetrahydrouridine inhibits the cytidine deaminase of normal cells to a greater extent than the cytidine deaminase of tumor cells – thereby selectively protecting the normal cells from the formation of the radiosensitizing and cytotoxic deaminated derivative. Thus, the claimed drug treatment not only sensitizes tumor cells to radiation treatment, but also improves the biochemical profile of both surviving tumor cells and surrounding tissue cells in such a manner as to improve the overall outcome for the patient. It would not have been obvious to one of skill in

the art that the claimed drug combination would have this paradoxical effect; that is, that it would increase the likelihood that tumor cells would die following radiation exposure, while also increasing the likelihood that cells that didn't die would have a more advantageous biochemical profile following treatment. Therefore, due to the current claim amendments, the instant claims are not obvious and these rejections should be withdrawn.

In view of the foregoing, it is submitted that the present application is now in condition for allowance. Reconsideration and allowance of the pending claims are requested. The Director is authorized to charge any fees or overpayment to Deposit Account No. 02-2135.

Respectfully submitted,

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